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EXAMINER	
RAWLINGS, STEPHEN L	
ART UNIT	**PAPER NUMBER**
1642	

DATE MAILED: 03/03/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/606,910	KARSTEN ET AL.	
	Examiner	Art Unit	
	Stephen L. Rawlings, Ph.D.	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 November 2004 and 01 February 2002*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *8-13 and 15-24* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *8-13 and 15-24* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *20020201*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: *Notice to Comply*.

DETAILED ACTION

1. The amendment filed November 30, 2004 is acknowledged and has been entered.

2. The amendment filed February 1, 2002 is acknowledged and has been entered. Claim 14 has been canceled. Claims 8-13 have been amended. Claims 15-24 have been added.

3. Claims 8-13 and 15-24 are pending in the application and are currently under prosecution.

4. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

5. The following Office action contains NEW GROUNDS of rejection.

Information Disclosure Statement

6. The information disclosure filed February 1, 2002 has been considered. An initialed copy is enclosed.

Grounds of Objection and Rejection Withdrawn

7. The amendment filed February 1, 2002 has obviated or rendered moot the grounds of objection and rejection set forth in the Office action mailed June 19, 2001.

Response to Amendment

8. Applicant's arguments with respect to claims 8-13 have been considered but are moot in view of the new ground(s) of rejection.

Specification

9. The disclosure is objected to for the following reason: The specification contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 C.F.R. § 1.821(a)(1) and (a)(2). Sequences appearing in the specification and/or drawings must be identified by sequence identifier in accordance with 37 C.F.R. 1.821(d). According to 37 CFR § 1.821(a), an unbranched sequence of four or more specifically identified amino acids or an unbranched sequence of ten or more nucleotides must be identified by sequence identification numbers. See MPEP § 2422.01.

In this instance, the sequence recited in claims 8, 10-13, and 15-18 is not identified. Additional sequences in the specification that are not identified include those disclosed at page 2, line 24; page 3, lines 4, 6, 8, 12, and 16; page 4, lines 2 and 12; and page 5, lines 6 and 21.

Applicant must provide appropriate amendments the specification, including the claims, inserting the required sequence identifiers. As noted in the attached Notice to Comply, appropriate action correcting this deficiency is required. If necessary to correct the deficiency, Applicant must submit paper and computer-readable copies of a substitute sequence listing, together with a statement that the content of both copies are the same and, where applicable, include no new matter.

10. The abstract of the disclosure filed February 1, 2002 is objected to it does not commence on a separate sheet in accordance with 37 CFR 1.52(b)(4). A new abstract of the disclosure is required and must be presented on a separate sheet, apart from any other text.

Claim Rejections - 35 USC § 112

11. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make

and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

12. Claims 8-13 and 15-24 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

This is a "written description rejection".

The considerations that are made in determining whether a claimed invention is supported by an adequate written description are outlined by the published Guidelines for Examination of Patent Applications Under the 35 U.S.C. 112, para. 1, ``Written Description" Requirement (Federal Register; Vol. 66, No. 4, January 5, 2001). A copy of this publication can be viewed or acquired on the Internet at the following address: <http://www.gpoaccess.gov/>.

Claims 8-13 and 15-24 are directed to peptides comprising the amino acid sequence set forth as SEQ ID NO: 3 (i.e., PDTRPAP), which are glycosylated at the threonine residue of said amino acid sequence.

Given the broadest reasonable interpretation, the claims embrace a genus of peptides that comprise SEQ ID NO: 3 but otherwise vary substantially in structure and function.

The recited common structural property (i.e., SEQ ID NO: 3) of the members of the genus of polypeptides encompassed by the claims is not related to any particularly identifying functional feature that is also shared by at least a substantial number of the members of the genus of polypeptides.

Accordingly, the specification fails to disclose a correlation between a particularly identifying structural feature that is shared by the members of the genus and a particularly identifying functional feature that is common among at least a substantial number of those members. Because the structure and function of the members of the genus of peptides to which the claims are directed vary substantially in structure and function, the peptide consisting of SEQ ID NO: 3 is not representative of the genus as a

whole. Therefore, absent a detailed description of at least most of the structurally and functionally disparate peptides encompassed by the claims, the skilled artisan could not immediately envision, recognize, or distinguish the members of the claimed genus and thus the supporting disclosure would not reasonably convey to the skilled artisan that Applicant had possession of the claimed invention at the time the application was filed.

Guidelines for Examination of Patent Applications Under the 35 U.S.C. 112, paragraph 1, ``Written Description" Requirement (*supra*) states, "[p]ossession may be shown in a variety of ways including description of an actual reduction to practice, or by showing the invention was 'ready for patenting' such as by disclosure of drawings or structural chemical formulas that show that the invention was complete, or by describing distinguishing identifying characteristics sufficient to show that the applicant was in possession of the claimed invention" (*Id.* at 1104). Guidelines further states, "[f]or inventions in an unpredictable art, adequate written description of a genus which embraces widely variant species *cannot* be achieved by disclosing only one species within the genus" (Id. at 1106); accordingly, it follows that an adequate written description of a genus cannot be achieved in the absence of a disclosure of at least one species within the genus. Because the claims encompass a genus of variant species, an adequate written description of the claimed invention must include sufficient description of at least a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics sufficient to show that Applicant was in possession of the claimed genus. However, factual evidence of an actual reduction to practice has not been disclosed by Applicant in the specification; nor has Applicant shown the invention was "ready for patenting" by disclosure of drawings or structural chemical formulas that show that the invention was complete; nor has Applicant described distinguishing identifying characteristics sufficient to show that Applicant had possession of the claimed invention at the time the application was filed.

This issue can be remedied by amending the claims, such that the breadth of the claims is limited to a peptide consisting of SEQ ID NO: 3, or alternatively limited to a peptide having or retaining a particularly identifying functional property of a peptide

comprising SEQ ID NO: 3 that correlates with a particularly identifying structural feature shared by the peptide of SEQ ID NO: 3 and at least a substantial number of the other peptides encompassed by the claims.

13. Claims 8-13 and 15-24 are rejected under 35 U.S.C. 112, first paragraph, because the specification, **while being enabling for making and using** a glycosylated or non-glycosylated peptide consisting of the amino acid sequence set forth as SEQ ID NO: 3, a glycosyated or non-glycosylated peptide consisting of the amino acid sequence set forth as SEQ ID NO: 1, and a glycosyated or non-glycosylated peptide consisting of the amino acid sequence set forth as SEQ ID NO: 2, wherein said peptides are glycosylated at the threonine residue of SEQ ID NO: 3 contained therein, **does not reasonably provide enablement for making and using** peptides comprising the amino acid sequence of SEQ ID NO: 3, a tumor vaccine comprising at least one of said peptides, a process for combating tumor cells of MUC1 positive carcinomas in a human comprising administering to the human a therapeutically effective amount of at least one of said peptides, or a process for immunizing a human against a mammary, colorectal or pancreatic carcinoma comprising administering to the human a therapeutically effective amount of at least one of said peptides. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

This is "a scope of enablement rejection".

The amount of guidance, direction, and exemplification disclosed in the specification would not be sufficient to enable the skilled artisan to make and use the claimed invention without a need to perform an undue amount of additional experimentation.

Factors to be considered in determining whether undue experimentation is required are summarized in *Ex parte Forman*, 230 USPQ 546 (BPAI 1986). These factors include the nature of the invention, the state of the prior art, the relative skill of those in the art, the amount of direction or guidance disclosed in the specification, the presence or absence of working examples, the predictability or unpredictability of the

art, the breadth of the claims, and the quantity of experimentation which would be required in order to practice the invention as claimed.

The specification teaches synthetic peptides consisting of the amino acid sequence of either SEQ ID NO: 1 or SEQ ID NO: 2, which are glycosylated at the tenth position (i.e., the second threonine residue), bind with increased affinity to monoclonal antibodies A76-A/C7 and MFO6, as compared to non-glycosylated peptides of the same sequences; see, e.g., page 4, line 1, through page 6, line 6. Both peptides comprise the amino acid sequence set forth as SEQ ID NO: 3; the aforementioned glycosylated threonine residue is contained in this sequence.

Furthermore, the prior art (e.g., Karsten et al. (*Cancer Res.* 1998 Jun 15; **58** (12): 2541-2549) teaches "MUC1 tandem repeat peptides", which comprise SEQ ID NO: 3 and are glycosylated at the threonine residue of SEQ ID NO: 3; see entire document (e.g., page 2542, Table 2). These peptides are derived from the "VNTR" domain of MUC1, which comprise a variable number of tandem repeats of the same amino acid sequence.

However, as explained above, claims 8-13 and 15-24 are directed to a genus of peptides that comprise the amino acid sequence of SEQ ID NO: 3 but which otherwise vary markedly in both structure and function.

Although methods for isolating other nucleic acid molecules comprising polynucleotide sequences that encode peptides having the recited structural feature are conventional in the art (e.g., hybridization assays), because the claims are not limited to peptides consisting of the amino acid sequence of SEQ ID NO: 3 or to peptides having any particular function, and moreover because the claimed peptides do not necessarily have or retain any particular function of the peptide of SEQ ID NO: 3, the skilled artisan would be left to discover a use for the claimed invention. Discovering a use for claimed peptides that do not have or retain a recited function falls into the realm of undue experimentation, since one would first have to characterize the activities or functions of the peptides and then develop methods for using the peptides, depending upon those activities or functions realized.

Furthermore, not all peptides comprising the amino acid sequence of SEQ ID NO: 3 are reasonably expected to have a function that is equivalent to the function of the peptide of SEQ ID NO: 3, particularly since the peptides are not necessarily fragments of MUC1.

Skolnick et al. (*Trends in Biotechnology* 2000; **18**: 34-39), for example, discloses that the skilled artisan is well aware that assigning functional activities for any particular protein or protein family based upon sequence homology is inaccurate, in part because of the multifunctional nature of proteins (see, e.g., the abstract; and page 34, *Sequence-based approaches to function prediction*). Even in situations where there is some confidence of a similar overall structure between two proteins, only experimental research can confirm the artisan's best guess as to the function of the structurally related protein (see, in particular, the abstract and Box 2).

In addition, Bowie et al. (*Science* 1990; **257**: 1306-1310) teaches that an amino acid sequence encodes a message that determines the shape and function of a protein; and, that it is the ability of these proteins to fold into unique three-dimensional structures that allows them to function and carry out the instructions of the genome. Bowie et al. teaches that the determination of protein structure from sequence data and, in turn, utilizing structural determinations to ascertain functional aspects of the protein is extremely complex (page 1306, column 1). Even if the skilled artisan were able to submit a complete list of the possible peptides, which fall within the scope of the claims, the skilled artisan could not recognize which of these would function similarly to a peptide consisting of SEQ ID NO: 3, and which would not. Thus, one skilled in the art would not accept an assertion, which is based only upon an observed commonality of seven contiguous amino acids, that a peptide comprising SEQ ID NO: 3 is functionally equivalent to the peptide of SEQ ID NO: 3.

Accordingly, the function of a peptide comprising SEQ ID NO: 3 cannot be reliably and accurately predicted; rather, the functions of the claimed peptides can only be determined empirically. Empirically determining whether these peptides have or retain the function of the polypeptide of SEQ ID NO: 3, or discovering that the peptides have other unique functions, constitutes additional, undue experimentation.

Claims 19 and 20 are drawn to a tumor vaccine comprising at least one member of a genus of peptides comprising the amino acid sequence of SEQ ID NO: 3 but which otherwise vary markedly in both structure and function; and claims 21-24 are drawn to processes for combating "MUC1 positive carcinomas" in humans or immunizing humans against mammary, colorectal or pancreatic carcinomas by administering to the humans a therapeutically effective amount of one or more of such structurally and functionally disparate peptides comprising SEQ ID NO: 3.

The State of the Prior Art:

The art of cancer prevention is intractable. Certainly, in view of this fact, one's success in practicing the invention would be unpredictable without first performing undue experimentation. Considering the state of the art, in the absence working exemplification, there cannot be a reasonable expectation of success in using the claimed invention in *preventing or suppressing* cancer in a patient.

Additionally, certainly not all patients are to be considered for prophylactic therapy, because only some patients will have a potential to benefit from such therapy. Certain antigenic peptides may not be displayed in the context of every class I Major Histocompatibility Complex (MHC) or in other words, bind to every type of HLA molecule. Thus, only patients with a particular HLA type will have a potential to benefit from the use of the invention. However, due to allelic variation in the population, not all patients of any given HLA type will necessarily be capable of benefiting from the use of the invention, because some HLA subtypes will not bind an immunogenic peptide produced as a result of vaccination with the claimed invention and therefore a cancer-specific CTL response will not be elicited.

For example, Yamshchikov et al. (*Clinical Cancer Research* 2001; **7**: 909s-916s) teaches that three of four HLA-A3 typed patients, each diagnosed with rapidly progressing melanoma, had no detectable CTL response following vaccination with an immunogenic peptide. Not surprisingly, the one patient that did have peptide-responsive CTL was the long-term surviving melanoma patient, i.e., Patient VMM18 from whom the peptide was originally isolated. Because the peptide was isolated from

the tumor-infiltrating lymphocytes (TIL) recovered from a tumor-involved nodal biopsy, lymphocytes isolated from the nodal biopsy would, of course, be expected to respond to peptide stimulation *in vitro*. Less understandably, despite the other patients being HLA-A3+, none of the lymphocytes isolated from their nodal biopsies responded *in vitro*. Obviously, the presence of HLA-A3 type class I MHC molecules is not the only criterion that determines whether an individual should be treated using the invention. Accordingly, there is insufficient guidance in the specification to enable one skilled in the art to use the invention, because the specification fails to disclose a means for selecting appropriate candidates for treatment using the invention and undue experimentation would be required to determine whether an individual candidate is appropriate.

Cytotoxic T cells (CTL) bind to antigen-presenting cells (APC) and under specific circumstances will become activated. Simplistically, the CTL and the APC interface by the highly specific formation of a trimolecular complex comprising the antigenic peptide "primed"-class I MHC molecule, displayed at the surface of the APC, and the T cell receptor (TCR), displayed at the surface of the CTL. Every individual has a relatively unique "repertoire" of T cells or clones, where each clone has a different TCR, which has a different antigenic binding specificity. Thus, some individuals' repertoires may be deficient in one or more CTL that, if present would be activated by the claimed immunogen. Those patients lacking the appropriate CTL clone will not benefit from the prophylactic or therapeutic use of the invention. Thus, within the population of HLA-typed patients, some will not respond because they have the "wrong" HLA subtype, which does not bind the claimed immunogenic peptide, some will fail to respond because their repertoire of lymphocytes is incomplete, and still others will fail for both of these reasons. Because the specification does not disclose which HLA subtypes and which TCR types will bind the immunogens produced as a result of an individual's immunization with the claimed invention, the specification fails to provide a means to identify the population of individuals with whom the invention can be used and thus, fails to provide an enabling disclosure. Again, one skilled in the art cannot use the invention with a reasonable expectation of success without first selecting an appropriate individual

for treatment and undue experimentation would be required to determine which population of individuals are appropriate.

The art of cancer immunotherapy is highly unpredictable, as evidenced, for example, by Bocchia et al. (*Haematologica*. 2000; **85**: 1172-1206). Bocchia et al. teaches that cancer vaccines, including those derived from MUC1 cannot be presently used without further undue experimentation; so, in the absent of exemplification that is reasonably commensurate in scope with the claims, the skilled artisan would not accept the assertion that the claimed invention can be used effectively to treat an individual diagnosed with a tumor, such as a MUC1 positive carcinoma, including breast, colorectal, or pancreatic carcinomas.

With regard to antitumor immunotherapy, Bodey et al. (*Anticancer Research* 2000; **20**: 2665-2676) teaches, "while cancer vaccine trials have yielded tantalizing results, active immunotherapy has not yet become an established modality of anticancer therapy" (page 2665, column 2). As to the current state of the art, Bodey et al. comment, "the use of active specific immunotherapy (ASI) for cancer (cancer 'vaccines') is still in its scientific infancy despite several decades of clinical and basic research" (page 2668, column 2). Bodey et al. discloses, "ASI in at least one instance may have cured melanoma in a patient with metastatic disease, but that patient developed another immunologically and genetically distinct melanoma" (page 2668, column 2). In the abstract Bodey et al. speculate upon the reasons that ASI is ineffective or lacks efficacy:

> The theoretical basis for all of these approaches is very well founded. Animal models, albeit highly artificial, have yielded promising results. Clinical trials in humans, however, have been somewhat disappointing. Although general immune activation directed against the target antigens contained with a cancer vaccine has been documented in most cases, reduction in tumor load has not been frequently observed, and tumor progression and metastasis usually ensue, possibly following a slightly extended period of remission. The failure of cancer vaccines to fulfill their promise is due to the very relationship between host and tumor: through a natural selection process the host leads to the selective enrichment of clones of highly aggressive neoplastically transformed cells, which apparently are so dedifferentiated that they no longer express cancer cell specific molecules. Specific activation of the immune system in such cases only leads to lysis of the remaining cells expressing the particular TAAs [tumor associated antigens] in the context of the particular human leukocyte antigen (HLA) subclass and the necessary

costimulatory molecules. The most dangerous clones of tumor cells however lack these features and thus the cancer vaccine is of little use.

The goal of tumor vaccination is the induction of tumor immunity to prevent tumor recurrence and to eliminate residual disease. However, Ezzell (*Journal of NIH Research* 1995; **7**: 46-49) states that tumor immunologists are reluctant to place bets on which cancer vaccine approach will prove effective in the long run (see the entire document, particularly last paragraph). Ezzell further teaches that no one is very optimistic that a single peptide will trigger an immune response strong enough to eradicate tumors or even to prevent the later growth of micro-metastases among patients whose tumors have been surgically removed or killed by radiation or chemotherapy (page 48, paragraph 6). More recently, Bodey et al. (cited *supra*) states, "there should be caution about assuming that a single epitope or even a few epitopes combined will be as effective 'crude' materials, which might better be thought of as 'polyvalent'" (page 2668, column 2). Spitler (*Cancer Biotherapy* 1995; **10**: 1-3) recognizes the lack of predictability of the nature of the art when she states, "ask practicing oncologists what they think about cancer vaccines and you're likely to get the following response: 'cancer vaccines don't work'. Ask a venture capitalist or the director of product development at a large pharmaceutical company and you're likely to get the same response" (page 1, paragraph 1).

Whatever avenue the artisan takes, in view of the unpredictability in the art, the rarity and lack of uniformity in the successful application, and the numerous and substantial limitations encountered, the threshold of enablement is high. The specification must enable one of skill in the art to make and to use the invention successfully without a need to first perform an undue amount of additional experimentation. To have success, the use of the invention must elicit a cancer-specific CTL response against the polypeptide of SEQ ID NO: 14 or a variant thereof. Boon (*Advances in Cancer Research*. 1992; **58**: 177-210) teaches that for successful application of active immunization in human patients, we have to stimulate immune defenses of organisms that have often carried a large tumor burden. Establishment of immune tolerance may therefore have already occurred in the patient and in such

cases, active specific immunization will be fruitless, since anergic TCL cannot be activated, will not proliferate, and are deficient in effector function. Several lines of evidence suggest that large tumor burdens can tolerize, or at least depress the capability to respond against the tumor (page 206, paragraph 2).

There is considerable art indicating that cancer vaccines are ineffective, *even if antigen-specific T-lymphocytes can be activated by immunization protocols*. Lee et al. (*Journal of Immunology* 1999; **163**: 6292-6300) teaches, "although comparative ex vivo sensitization of pre- and postvaccination PBMC [peripheral blood mononuclear cells, such as B- and T-lymphocytes] has identified reproducible, vaccine-specific systemic T cell responses to immunization, in the majority of cases no regression is seen" (page 6292, column 1). In studies similar to those that are set forth in the examples in the specification, Lee et al. teaches that melanoma antigen epitopes were identified and that these peptide epitopes were capable of inducing highly specific T cell responses against autologous and some HLA-matched tumor cells. Lee et al. discloses, "these studies gave the impression that vaccines induce powerful immunizations comparable to those demonstrable against common pathogens such as the influenza virus to which individuals are repeatedly exposed throughout their lifetime". However, "in most cases, this **vaccine-induced T cell reactivity still does not lead to tumor regression**" (emphasis added) (page 6299, column 1). One of the reasons for the discrepancy, Lee et al. suggest, may be that in vitro methods, which are commonly used to assess immune post-vaccination immune response, such as cell-mediated cytotoxicity assays, tend to "overestimate quantitatively the strength of the immune reaction within the organism" (page 6299, column 1). Lee et al. catalogs a variety of possible explanations for the lack of efficacy, including clonal deletion, exhaustion, or senescence, which are implicated in the development of systemic, epitope-specific immune tolerance, and inadequate immune response attributable to decreased T cell receptor signaling capacity or circulating immune-suppressive cytokines, but conclude that their data suggest that the extent rather than the quality of the response might be more significant limitation of the vaccination protocol (page 6299, column 2). More specifically, Lee et al. reports, "we were surprised at the relatively low numbers of CTL precursors after

vaccination even in patients' samples that boasted an exceptional epitope-specific expansion in vitro" (page 6299, column 2). Lee et al. summarizes their study, teaching that "a peptide-based vaccine can effectively generate a quantifiable T cell-specific immune response in the PBMC of cancer patients, though such a response does not associate with a clinically evident regression of metastatic melanoma" (abstract). While Lee et al. refers specifically to the treatment of melanoma using a different epitope, the teachings are highly germane to the enablement issues relevant in the instant application, because the severe limitations will undoubtedly be shared by any protocol that uses the claimed invention, and there is no exemplification in the specification that would suggest otherwise. In yet another example, Zaks et al. (*Cancer Research.* 1998; **58**: 4902-4908) teaches that immunization of patients diagnosed with cancer with a peptide epitope derived from the tumor antigen HER-2/neu/ErbB2 leads to activation of peptide-specific cytotoxic T-lymphocytes, but that the T-lymphocytes fail to recognize tumor cells that express the antigen. Zaks et al. discloses that their experience is not unique (page 4907, column 2). Gao et al. (*Journal of Immunotherapy.* 2000; **23**: 643-653) found that although antitumor CTL response was enhanced by immunization, the tumors failed to regress. Gao et al. teaches that the lack of regression was associated with a lack of CTL migration to the tumor sites (abstract). Thus, activation of peptide epitope-specific CTL is not an appropriate endpoint and a prediction or estimation of efficacy based only upon such data is imprudent or inexact.

Summarizing reasons for the lack of successful application of immunotherapy, Bodey et al. teaches that despite promising, even tantalizing results *in vitro* and *in vivo*, especially with animal models, the failure of cancer vaccines is predicated by very relationship between the tumor and the host immune system, which effectively makes the use of cancer vaccines futile:

> Malignant tumors undergo constant microevolution. Natural selection of the most advantageous surface IP [immunophenotype] involves constant modulation of previous IPs. Progressive dedifferentiation characterizes all neoplastically transformed cells. During this process, numerous 'novel' cell surface antigens appear, are modified and thus do not present the host's immune system with some immunogenic elements. The leukocytic inflammatory infiltrate contains cells with divers capabilities including neutrophils, macrophages and other professional APCs [antigen-presenting cells], as well

> as T lymphocytes. In situ activation of TAA [tumor-associated antigen] specific CTL [cytotoxic T-lymphocyte] clones occurs and thousands of tumor cells are lysed. However, as we would expect from any population in danger of extinction, the cells of the neoplastically transformed mass proceed with their microevolution and numerous clones of tumor cells survive each repeated attack by the immune system through secretion of immunoinhibitory cytokines, downregulation of MHC molecules, loss of costimulatory molecules, and induction of clonal T cell anergy, among other as yet uncovered ways. This process continues until the 'creation' (ironically as it may sound, by the host's immune system) of highly resistant, poorly immunogenic, and extremely aggressive clones of tumor cells. This is the reality of cancer progression: a back-and-forth struggle between host and tumor, with evolutionary dynamic exchanges throughout the entire process. Use of cancer vaccines to stimulate the immune system may be in vain" (citations omitted) (pages 2673-2674).

The Relative Skill of those in the Art:

Although high, the relative skill of those in the art is such that, absent a sufficient disclosure to enable the use of the claimed invention, an undue amount of additional experimentation would need be performed before the claimed invention, commensurate in scope with the claims, could be made and used to prevent or treat a disease, including cancer, and more particularly either breast, colorectal, or pancreatic cancer.

The Amount of Direction or Guidance Disclosed in the Specification:

The specification only shows that peptides consisting of the amino acid sequences of SEQ ID NO: 1 or SEQ ID NO: 2, which are glycosylated at the tenth position, bind with increased affinity to two monoclonal antibodies relative to the non-glycosylated peptides. Although concluding that the glycosylated peptides have increased antigenicity (page 6, lines 8 and 9), the specification provides no factual evidence that reasonably supports such a conclusion, since the specification has not shown that the glycosylated peptides more effectively induce an immune response than the non-glycosylated peptides. The binding affinity of the glycosylated peptides toward the monoclonal antibodies is not reflective of the peptides ability to trigger an immune response.

The Presence or Absence of Working Examples:

The specification does not exemplify the use of the claimed invention to prevent or treat, a disease, including MUC1 positive carcinomas, and breast, colorectal and pancreatic cancer.

The Predictability or Unpredictability of the Art:

As evidenced by the teachings of the references cited above to address the level of skill in the art and the state of the art, now and as of the earliest filing date sought by Applicant in the instant application, the art is characterized by high level of complexity, as well as unpredictability.

Regarding the possibility that the claimed invention might be therapeutically useful, the art of drug discovery for is highly unpredictable. With regard to anticancer drug discovery, for example, Gura (*Science* 1997; **278**: 1041-1042) teaches that researchers face the problem of sifting through potential anticancer agents to find ones promising enough to make human clinical trials worthwhile (abstract). Gura teaches that since formal screening began in 1955, many thousands of drugs have shown activity in either cell or animal models, but that only 39 have actually been shown to be useful for chemotherapy (page 1041, first and second paragraphs). Moreover, because of the lack of predictability in the art, Gura discloses that often researchers merely succeed in developing a therapeutic agent that is useful for treating the animal or cell that has been used as a model, but which is ineffective in humans, indicating that the results acquired during pre-clinical studies are often non-correlative with the results acquired during clinical trials (page 1041, column 2).

Additionally, only certain immunogenic peptides comprising SEQ ID NO: 3 might be expected to effectively induce antigen-specific cytotoxic T lymphocytes (CTL) that will kill target cells; other immunogenic fragments will not be effective. Lu et al. (*Cancer Research* **62**: 5807-5812, 2002), for example, teaches that four of five immunogenic fragments of prostate-specific membrane antigen (PSMA) were capable of inducing antigen-specific CTL killing of target cells, but only one was effective at recognizing prostate tumor cells expressing the protein; see, e.g., the abstract. These results are reminiscent of the teachings of Lee et al. (cited *supra*) and Zaks et al. (cited *supra*).

Thus, while some of the claimed peptides may effective to stimulate a CTL-mediated response to the immunogenic fragment, the skilled artisan cannot predict which might be used successfully to treat or prevent a disease, including cancer.

The Breadth of the Claims:

Claims 8-13 and 15-24 are directed to a genus of peptides that comprise the amino acid sequence of SEQ ID NO: 3 but which otherwise vary markedly in both structure and function. Claims 19 and 20 are directed to a genus of "tumor vaccines" comprising one or more members of said genus of peptides for use in preventing or treating any member of a genus of tumors having widely varying etiologies and pathologies. Claims 21 and 22 are drawn to a genus of methods for "combating" any member of said genus of tumors that express MUC1 comprising administering a therapeutically effective amount of one or more members of said genus of peptides. Claims 23 and 24 are drawn to a genus of methods for immunizing a human against a genus of mammary tumors, a genus of colorectal tumors, or a genus of pancreatic tumors comprising administering a therapeutically effective amount of one or more members of said genus of peptides.

The Quantity of Experimentation Required:

As evidenced by the teachings of the references cited above to address the level of skill in the art and the state of the art, now and as of the earliest filing date sought by Applicant in the instant application, undue experimentation would have to be performed before the claimed invention, reasonably commensurate in scope with the claims, could be made and used successfully by the skilled artisan, since the skilled artisan cannot readily, that is, by routine experimentation alone, make glycosylated peptides comprising SEQ ID NO: 3, which can be used to prevent or treat a disease, such as cancer.

Further regarding the lack of predictability in using the claimed invention and thus the need to first perform undue experimentation before its use, Karsten et al. (*Cancer Res.* 1998 Jun 15; **58** (12): 2541-2549) teaches that, although evidence has been

obtained for a potential contribution of glycosylated epitopes on MUC1 in specific T cell reactions, "[w]hether the glycosylation-induced effects on the peptide antigenicity observed in the present study are related to this carbohydrate-mediated enhancement of cytotoxicity remains to be elucidated" (page 2549, column 1). As previously noted, however, any relationship between increased binding affinity of monoclonal antibodies toward the peptides and increased immunogenicity has not been previously described and perhaps has yet to be explored.

In summary, the specification does not exemplify, prophetically or otherwise, the use of the claimed invention to prevent or treat carcinomas in humans. In fact, the specification only shows that peptides consisting of the amino acid sequences of SEQ ID NO: 1 or SEQ ID NO: 2, which are glycosylated at the tenth position, bind with increased affinity to two monoclonal antibodies relative to the non-glycosylated peptides. Although concluding that the glycosylated peptides have increased antigenicity (page 6, lines 8 and 9), the specification provides no factual evidence that reasonably supports such a conclusion, since the specification has not shown that the glycosylated peptides more effectively induce an immune response than the non-glycosylated peptides. The binding affinity of the glycosylated peptides toward the monoclonal antibodies is not reflective of the peptides ability to trigger an immune response. Therefore, upon careful consideration of the factors used to determine whether undue experimentation is required, in accordance with *Ex parte Forman*, 230 USPQ 546 (BPAI 1986), a preponderance of factual evidence of record indicates that the amount of guidance, direction, and exemplification disclosed in the specification would not be sufficient to enable the skilled artisan to use the claimed invention without undue experimentation.

Claim Rejections – 35 USC § 102

14. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

15. Claims 8-13 and 15-20 are rejected under 35 U.S.C § 102(a) as being anticipated by Karsten et al. (*Cancer Res.* 1998 Jun 15; **58** (12): 2541-2549).

Claims 8-13 and 15-20 are drawn to a peptide or a composition thereof, wherein said peptide comprises the amino acid sequence of SEQ ID NO: 3 (i.e., a sequence of the human epithelial mucin MUC1) and is glycosylated at the threonine residue of SEQ ID NO: 3.

Karsten et al. teaches "MUC1 tandem repeat peptides", which comprise SEQ ID NO: 3 and are glycosylated at the threonine residue of SEQ ID NO: 3; see entire document (e.g., page 2542, Table 2). The peptides (e.g., peptides "A1" and "A12") are about 20 amino acids in length and are either α-N-acetylgalactosamine (GalNAc)- or Galβ1-3GalNAc-glycosylated at the threonine residue of SEQ ID NO: 3; see page 2542, Table 2. GalNAc is a monosaccharide; and Galβ1-3GalNAc is a disaccharide (i.e., an oligosaccharide). Karsten et al. teaches a composition comprising these peptides, which, absent a showing of any difference, further comprises "a pharmaceutically acceptable formuation"; see, e.g., page 2542, column 2.

16. Applicant cannot rely upon the foreign priority papers to overcome this rejection because a translation of said papers has not been made of record in accordance with 37 CFR 1.55. See MPEP § 201.15.

Conclusion

17. No claim is allowed.

18. The prior art made of record and not relied upon is considered pertinent to Applicant's disclosure. U.S. Patent No. 6,465,220 teaches a glycosylated peptide comprising an amino acid sequence of the MUC1 that is identical to the amino acid sequence set forth as SEQ ID NO: 3, which has a length of at least about 20 amino

acids but which is not glycosylated at the threonine residue of SEQ ID NO: 3; see entire document (e.g., columns 9 and 10, Table 1).

19. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Stephen L. Rawlings, Ph.D. whose telephone number is (571) 272-0836. The examiner can normally be reached on Monday-Friday, 8:30AM-5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Siew can be reached on (571) 272-0787. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Stephen L. Rawlings, Ph.D.
Examiner
Art Unit 1642

slr
February 18, 2005

Notice to Comply	Application No.	Applicant(s)	
	09/606,910	KARSTEN ET AL.	
	Examiner	Art Unit	
	Stephen L. Rawlings, Ph.D.	1642	

NOTICE TO COMPLY WITH REQUIREMENTS FOR PATENT APPLICATIONS CONTAINING NUCLEOTIDE SEQUENCE AND/OR AMINO ACID SEQUENCE DISCLOSURES

Applicant must file the items indicated below within the time period set the Office action to which the Notice is attached to avoid abandonment under 35 U.S.C. § 133 (extensions of time may be obtained under the provisions of 37 CFR 1.136(a)).

The nucleotide and/or amino acid sequence disclosure contained in this application does not comply with the requirements for such a disclosure as set forth in 37 C.F.R. 1.821 - 1.825 for the following reason(s):

☒ 1. This application clearly fails to comply with the requirements of 37 C.F.R. 1.821-1.825. Applicant's attention is directed to the final rulemaking notice published at 55 FR 18230 (May 1, 1990), and 1114 OG 29 (May 15, 1990). If the effective filing date is on or after July 1, 1998, see the final rulemaking notice published at 63 FR 29620 (June 1, 1998) and 1211 OG 82 (June 23, 1998).

☐ 2. This application does not contain, as a separate part of the disclosure on paper copy, a "Sequence Listing" as required by 37 C.F.R. 1.821(c).

☐ 3. A copy of the "Sequence Listing" in computer readable form has not been submitted as required by 37 C.F.R. 1.821(e).

☐ 4. A copy of the "Sequence Listing" in computer readable form has been submitted. However, the content of the computer readable form does not comply with the requirements of 37 C.F.R. 1.822 and/or 1.823, as indicated on the attached copy of the marked -up "Raw Sequence Listing."

☐ 5. The computer readable form that has been filed with this application has been found to be damaged and/or unreadable as indicated on the attached CRF Diskette Problem Report. A Substitute computer readable form must be submitted as required by 37 C.F.R. 1.825(d).

☐ 6. The paper copy of the "Sequence Listing" is not the same as the computer readable from of the "Sequence Listing" as required by 37 C.F.R. 1.821(e).

☒ 7. Other: If necessary to correct the deficiency described in the Office action, Applicant should provide substitute copies of the sequence listing and the statement, as indicated below.

Applicant Must Provide:

☐ An initial or substitute computer readable form (CRF) copy of the "Sequence Listing".

☐ An initial or substitute paper copy of the "Sequence Listing", as well as an amendment directing its entry into the specification.

☐ A statement that the content of the paper and computer readable copies are the same and, where applicable, include no new matter, as required by 37 C.F.R. 1.821(e) or 1.821(f) or 1.821(g) or 1.825(b) or 1.825(d).

For questions regarding compliance to these requirements, please contact:

For Rules Interpretation, call (703) 308-4216
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